REMARKS

The Office Action and the cited and applied reference have been carefully reviewed. No claim is allowed. Claims 93-119 presently appear in this application and define patentable subject matter warranting their allowance. As claim 97, which was not amended in the amendment filed November 30, 2001, was previously indicated as being allowed and is now indicated as being rejected, applicants request that the finality of this Office Action be withdrawn. Reconsideration and allowance are hereby respectfully solicited.

Claims 93-118 remain rejected and claim 119 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is respectfully traversed.

The examiner states that claim 93 remains indefinite for reciting the term "substantially the same" because it relates to an amino acid sequence. Applicants believe that this issue is obviated by the amendment to claim 93 where it is now clear that the "substantially the same" physiochemical properties (1) to (3) do not include the amino acid sequence.

With regard to claim 94, it is submitted that when the temperature is not specifically disclosed, it is understood by those of skill in the art that the temperature is ambient (room) temperature and therefore claim 94 is not indefinite.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 93, 94, 96, 118 and dependent claims 95 and 98-117 remain rejected under 35 U.S.C. §112, first paragraph, as the examiner states that enablement is not commensurate in scope with the claims for the reasons cited in the last Office Action, paper no. 22. Claims 93-96 and 98-118 remain rejected under 35 U.S.C. §112, first paragraph, as lacking written description for the variants of SEQ ID NO:2 and as not conveying to those skilled in the art that the inventors were in possession of the genus of "mammal" IL-18 at the time the application was filed. These rejections are respectfully traversed.

It should be noted that "variants of SEQ ID NO:2" are defined in claim 93 by the following two conditions.

(a) the variants must have substantially the same physicochemical properties of (1) to (3) as the protein (i), and

(b) the variants must have an amino acid sequence of SEQ ID NO:2 in which one or more amino acids are replaced with different amino acids, one or more amino acids are added to the N-terminus of SEQ ID NO:2, or one or more amino-acids at the N-terminus of SEQ ID NO:2 are deleted. Claim 93 does not broadly claim all the antibodies which specifically recognize any variants of SEQ ID NO:2, but rather claims a monoclonal antibody which specifically recognizes such variants as defined by the above two conditions.

Applicants submit that it should be easy for a skilled artisan to obtain "variants of SEQ ID NO:2" as defined in claim 93 based on the amino acid sequence of SEQ ID NO:2 which had been

identified by the present inventors. In addition, it should also be easy for a skilled artisan to obtain an antibody, in particular a monoclonal antibody, of the thus obtained "variants of SEQ ID NO:2" using the variants as antigen, even if the specification does not disclose concrete examples. Furthermore, a skilled artisan would readily understand that such antibody as mentioned above has the same use as antibodies against the protein having the amino acid sequence of SEQ ID NO:2. Applicants therefore believe that enablement provided by the present specification is commensurate in scope with claim 93.

With regard to the lack of description rejections, applicants submit that a protein of the present invention is one which has an interferon-gamma (IFN-γ) inducing activity. It is well-known that IFN-γ exists widely in mammal. This means that there is a substance in mammals which induces the production of IFN-γ. While this does not necessarily mean that the same IFN-γ inducing substance is in all mammals, it would be expected by a skilled artisan that mammals other than mice would have the same or similar IFN-γ inducing substance as the IFN-γ inducing protein discovered by the present inventors in mice.

Furthermore, the present inventors had isolated the IFN-γ inducing protein, determined its amino acid sequence, and established a monoclonal antibody which recognizes the substance. Accordingly, the present invention is a pioneer invention with regard to IFN-γ inducing substance, and applicants believe that "IGIF or IL-18 is obtainable from a mammal" in claim 95 should be

acknowledged as an invention that is broader that just what is obtained in mice; otherwise, the present invention would be unfairly restricted.

Claims 93-118 remain rejected and newly submitted claim 119 is rejected under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al. (1993) for the reasons cited in the last Office Action, paper no. 22, at pages 6-8. This rejection is respectfully traversed.

While Okamura, which is applied by the examiner as a subsequent study, refers to the relationship between IGIF having the molecular weight of 18-19 kDa and the factor disclosed in Nakamura as having a molecular weight of 75 kDa, Okamura never states that they are the same. Correctly speaking, Okamura states that IGIF having the molecular weight of 18-19 kDa is contained in the factor of Nakamura. The examiner's attention is invited to the description at page 3966, left column to page 3966 right column of Okamura, in particular, page 3966 right column, the last sentence of the first paragraph, where Okamura states:

> The serum factor whose apparent molecular mass was previously found to be 75 kDa by gel filtration was shown to <u>contain</u> the same 18- to 19-kDa IGIF. (emphasis added)

It is apparent that the factor of Nakamura is a mixture of IGIF and other substances. However, Nakamura <u>did not recognize</u> the presence of IGIF at all and naturally <u>did not separate</u> IGIF to which Okamura refers. It is therefore believed that it would have been difficult even for one of skill in the art to recognize and

successfully separate IGIF based on the teaching disclosed in Nakamura, even if the factor of Nakamura contains IGIF. Applicants submit that the presently claimed invention cannot be made obvious over Nakamura et al.

The examiner also states that the factor of Nakamura lost its IFN-γ inducing activity in treatment on SDS-PAGE because a reducing agent, 2-mercaptoethanol, is used in Nakamura. The examiner also further states that IGIF maintains its IFN-γ inducing activity in treatment on SDS-PAGE because the treatment is conducted under non-reducing condition without using a reducing agent, 2-mercaptoethanol.

The examiner's attention is respectfully invited to the passage at page 67, lines 4-5 of Nakamura, where it is disclosed that

> Treatment with 2-mercaptoethanol resulted in augmented ability to induce IFN-γ.

In addition, Nakamura at page 67, table 2, shows that 2-mercaptoethanol enhances the IFN-γ inducing ability of Nakamura's factor. It is therefore believed that those of skill in the art would have understood from these disclosures of Nakamura that the IFN-γ inducing ability of Nakamura's factor should be enhanced and not lost by the addition of 2-mercaptoethanol.

Applicants believe that the IGIF protein recited in the present claims is clearly distinguished from the factor of Nakamura in IFN-γ inducing activity after SDS-PAGE and is therefore unobvious over Nakamura.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

Claim 93 has been amended as follows:

93(Twice-amended). A monoclonal antibody which specifically recognizes (i) an interferon-gamma (IFN-γ) inducing protein, also known as IGIF and IL-18, having the following physiochemical properties of (1) to (4) or (ii) a variant thereof which has substantially the same physicochemical properties of (1) to (3) as the protein of (i) ~~but~~ and has an amino acid sequence of SEQ ID NO:2 in which one or more amino acids are replaced with different amino acids, one or more amino acids are added to the N- or C-terminus of SEQ ID NO:2, or one or more amino acids at the N- or C-terminus of SEQ ID NO:2 are deleted:

(1) Molecular weight

19,000 ± 5,000 daltons on gel filtration and sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE);

(2) Isoelectric point (pI)

4.8 ± 1.0 on chromatofocusing;

(3) Biological activity

Inducing the interferon-γ production by immunocompetent cells; and

(4) Partial amino acid sequence

Possessing ~~a part of the whole of~~ the amino acid sequence of SEQ ID NO:2, wherein Xaa is Met or Thr.